REMARKS

Telephone Interview

Applicants express their appreciation to Examiner Xie and Examiner Nickol for the courtesy extended to Applicants' representative, Angela Dallas Sebor, during the telephone interview of November 1, 2006. During the interview, the Examiners and Dr. Sebor discussed the pending rejections of the claims under 35 U.S.C. § 102 and § 103. Dr. Sebor discussed in more detail the position that neither of Sytkowski et al. (WO 99/02709) or Sytkowski et al. (U.S. Patent No. 6,242,570) enables one of skill in the art to make a direct fusion between EPO and IgG-Fc or between two EPO proteins, because since Sytkowski et al. clearly did not fully appreciate the structure of a direct fusion of EPO and IgG-Fc domains, it is impossible to use the method taught in Sytkowski et al. to construct such a protein. To attempt to use the method described by Sytkowski et al., one would have to either insert a linker or change the amino acid sequences at the joined ends of the protein (which results in the creation of a linker and further modifies the joined proteins). Moreover, the lack of teaching in either reference with respect to fusion proteins containing a linker was discussed. Applicants' agent additionally proposed to limit certain claims to the embodiment of an EPO-Ig fusion protein and to consider adding functional/activity limitations to certain claims. Agreement was not reached on any of the pending claims, but the Examiners indicated that new amendments and arguments would be carefully considered.

Amendments to the Claims

Claims 67, 87, 89, and 90, have been amended to be restricted to the elected species of erythropoietin.

Claim 89 has been amended to recite a positive step for the method claim, which is supported on page 10, lines 8-10.

Claim 105 has been amended to correct the improper antecedent basis, and is supported on page 6, lines 20-23.

New Claim 125 is supported by prior Claim 67 and in the specification, page 3, lines 26-28; page 3, lines 3-9 and Example 4.

New Claim 126 is supported by prior Claim 67 and in the specification, page 8, lines 13-15 and Example 4.

New Claim 127 is supported by Examples 1-4.

New Claim 128 is supported in the specification on page 8, lines 13-15 and Example 4.

New Claim 129 is supported in the specification on page 6, lines 8-10, and Example 4.

New Claim 130 is supported by prior Claim 68.

New Claim 131 is supported by prior Claims 90 and 92 and Example 4.

New Claim 132 is supported by prior Claims 90 and 92 and Example 4.

New Claim 133 is supported by prior Claims 90 and 92 and Examples 1-3.

New Claim 134 is supported by prior Claim 90, page 8, lines 15-18 and Examples 1-3.

New Claim 135 is supported by prior Claim 90, page 8, lines 15-18 and Examples 1-3.

New Claim 136 is supported by prior Claim 90, and on page 6, lines 8-10 and Examples 1-3.

New Claim 137 is supported by prior Claim 67, and on page 8, lines 15-18, and Example 4.

New Claim 138 is supported by prior Claim 94.

Any other amendments not expressly discussed are believed to be clerical in nature.

Objection to the Claims

The Examiner has objected to Claims 76, 103, 116 and 122 as containing subject matter directed to non-elected inventions. These claims have been cancelled, without prejudice to or disclaimer of the subject matter therein and accordingly, the objection is now moot.

Rejection of Claims 70 and 96 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 70 and 96, contending that these claims are indefinite because the recited EC_{50} is alleged to vary depending on what assay system is used.

In reply, Claim 70 has been cancelled, without prejudice to or disclaimer of the subject matter therein and accordingly, this rejection is moot. Claim 96 has been amended to recite that the EC_{50} is measured using a human UT7/epo cell line that proliferates in response to EPO,

which is described in detail in the present specification. New Claims 126, 128, 134, 135, 136 and 137 also recite this cell line.

In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 70 and 96 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 67-60 and 77-84 Under 35 U.S.C. § 102(a):

The Examiner has rejected Claims 67-70 and 77-84 under 35 U.S.C. 102(a), contending that these claims are anticipated by PCT Publication No. WO 99/02709 to Sytkowski et al. The Examiner contends that WO 99/02709 teaches fusions between erythropoietin (EPO) or EPO-like molecules and Ig polypeptide chains. The Examiner asserts that there is no limitation on the sequence of the fusion proteins and that therefore, WO 99/02709 is enabling for the production of a fusion between EPO or EPO-like molecules and an Ig without an intervening peptide linker.

Applicants traverse the rejection of Claims 67-70 and 77-84 under 35 U.S.C. § 102(a). Initially, it is noted that Claims 69-70 and 79 have been cancelled, without prejudice to or disclaimer of the subject matter therein, and therefore, rejection of these claims is now moot.

Applicants submit that PCT Publication No. WO 99/02709 is not effective prior art against the invention as claimed in pending Claims 67, 68, 77, 78 or 80-84, or of any new Claims 125-129, because the claimed subject matter was invented by the present inventors prior to the effective date of PCT Publication No. WO 99/02709, which is the publication date, January 21, 1999. Enclosed herewith is a Declaration under 37 CFR § 1.131 executed by both of the present inventors. This Declaration provides evidence of conception of the invention as claimed in these claims at a date prior to January 21, 1999, followed by diligence beginning from a date prior to January 21, 1999, to the constructive reduction to practice of the invention as claimed in Claims 67, 68, 77, 78, 80-84, and 125-129. Further evidence of continued diligence, followed by actual reduction to practice can be demonstrated if necessary. In addition, the present application demonstrates actual and constructive reduction to practice of these embodiments of the invention. As required by 37 CFR § 1.131, the Declaration affirms that the acts relied upon to establish actual reduction to practice were carried out in the United States. Therefore, Applicants submit that PCT Publication No. WO 99/02709 is not an effective reference against the present

claims.

In addition, even if, *arguendo*, PCT Publication No. WO 99/02709 was an effective reference, as previously argued, Applicants maintain the position that WO 99/02709 does not actually teach an EPO-IgG fusion protein as claimed in Claim 67 as asserted by the Examiner, because the publication is non-enabling for the production of such a protein. To attempt to use the only method described by Sytkowski et al. for production of the fusion protein, one would have to either insert a linker or change the amino acid sequences at the joined ends of the protein (which results in the creation of a linker and further modifies the joined proteins). Accordingly, WO 99/02709 does not teach the fusion protein recited in Claim 67 and dependent claims therefrom. "In determining that quantum of prior art disclosure which is necessary to declare an applicant's invention 'not novel' or 'anticipated' within section 102, the stated test is whether a reference contains an 'enabling disclosure'..." *In re Hoeksema,* 399 F.2d 269, 158 USPQ 596 (CCPA 1968). The disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. *Elan Pharm., Inc. v. **>Mayo Found. For Med. Educ. & Research<*, 346 F.3d 1051, 1054, 68 USPQ2d 1373, 1376 (Fed. Cir. 2003). In the case of WO 99/02709, while this reference may name directly attaching an EPO protein to an Ig protein, the only method described for achieving EPO-Ig fusions in WO 99/02709 will result in the introduction of a linker or will otherwise change the amino acid sequence of EPO or the IgG domain to a non-natural sequence, which is effectively a linker, as set forth in the Declaration under 37 CFR 1.132 previously submitted. In contrast, the present inventors realized that a different method would be required to create a fusion protein without a linker, as compared to a fusion protein with a linker. Specifically, the inventors first created a fusion protein with a linker and then determined a method for deletion of the linker using *in vitro* mutagenesis methods while maintaining the biological activity of the fusion protein, to ensure that the claimed fusion proteins were truly fusions without a linker. This is not possible using the methods taught by Sytkowski et al.

In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 67-70 and 77-84 under 35 U.S.C. 102(a).

Rejection of Claims 106, 109, 110, 112, 113, and 116 Under 35 U.S.C. § 102(e):

The Examiner has rejected Claims 106, 109, 110, 112, 113 and 116 under 35 U.S.C. § 102(e), contending that these claims are anticipated by U.S. Patent No. 6,242,570 by Sytkowski et al., for the reasons of record.

In reply, Applicants note that Claims 106, 109, 110, 112, 113 and 116 have been cancelled, without prejudice to or disclaimer of the subject matter therein and therefore, this rejection is moot. Accordingly, the Examiner is respectfully requested to withdraw the rejection of Claims 106, 109, 110, 112, 113 and 116 under 35 U.S.C. § 102(e).

Rejection of Claims 90-96 and 102-104 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 90-96 and 102-104 under 35 U.S.C. § 103, contending that these claims are unpatentable over PCT Publication No. WO 99/02709 to Sytkowski in view of Mapelli (U.S. Patent No. 5,519,115). The Examiner contends that WO 99/02709 teaches fusion proteins between EPO and Ig having a flexible protein linker, but acknowledges that WO 99/02709 does not teach peptide linkers of 2, 4 of 7 amino acids comprised of serine and/or glycine. The '115 patent is cited as teaching that small bridges of 5 amino acids or less can be used to link monomers. The Examiner contends that it would have been obvious to combine the teachings of WO 99/02709 and the '115 patent to use small, glycine rich linkers to link EPO to Ig. In response to Applicants' prior arguments, the Examiner argues that the claims are not limited to EPO-Ig, but in response to the argument that linkers can have a profound impact on biological activity of proteins, the Examiner asserts that the '115 patent provides guidance for using linkers.

Applicants traverse the rejection of Claims 90-96 and 102-104 under 35 U.S.C. § 103. Initially, it is noted that claims 95 and 103 have been cancelled, without prejudice to or disclaimer of the subject matter therein. Accordingly, the rejection of these claims is moot.

Applicants submit that PCT Publication No. WO 99/02709 is not effective prior art against the invention as claimed in pending Claims 90-94, 96, 102 and 104, or of any new Claims 130-135, because the claimed subject matter was invented by the present inventors prior

to the effective date of PCT Publication No. WO 99/02709, which is the publication date, January 21, 1999. Referring again to the Declaration under 37 CFR § 1.131 executed by both of the present inventors, this Declaration provides evidence of conception and actual reduction to practice of the invention as claimed in Claims 90, 91 (in part), 92 (in part), 94 (in part), 96, 104, 130, 133, 134 and 135 at a date prior to January 21, 1999. The Declaration also provides evidence of conception of the invention as claimed in Claims 90-94, 96, 102, 104, and 130-135 at a date prior to January 21, 1999, followed by diligence beginning from a date prior to January 21, 1999, to the constructive reduction to practice of the invention as claimed in Claims 90-94, 96, 102 and 104, or of any new Claims 130-135. As required by 37 CFR § 1.131, the Declaration affirms that the acts relied upon to establish actual reduction to practice were carried out in the United States. Therefore, Applicants submit that PCT Publication No. WO 99/02709 is not an effective reference against the present claims. Mapelli et al. teaches the use of peptide linkers for the construction of a bridge to form *oligopeptides*, which are relatively small monomer peptides having antimicrobial activity that are linked together. This reference is not at all directed to the production of EPO-Ig fusion proteins, which is the fusion of two large proteins with very different structures. EPO-Ig fusion proteins are far more complex than the simple oligomers contemplated by the '115 patent, because EPO-Ig fusion proteins also interact to form disulfide-linked dimers, which can negatively affect their bioactivity. Accordingly, Mapelli et al. does not teach or suggest the presently claimed invention.

In addition, as previously argued and described in the prior Declaration of Dr. Cox under 37 CFR. 1.132, much of the literature, including that cited by the Examiner, teaches that peptide linkers should be longer than the presently claimed linkers. Applicants refer to prior arguments in the § 1.132 Declaration and the last-filed response, as well as the references of Robinson, Qui, and Chang for example. Therefore, the literature teaches that the length of the linker can dramatically impact the biological activity of the resulting fusion protein, and further teaches that longer peptide linkers than those presently claimed were generally preferred at the time of the invention, in contrast to the teachings and examples provided by the present inventors. The inventors have demonstrated the ability to produce the recited fusion proteins with substantially similar biological activities to the wild-type protein, which is not predicted by the combination of

references cited by the Examiner.

In view of the foregoing remarks, the Examiner is respectfully requested to withdraw the rejection of Claims 90-96 and 102-104 under 35 U.S.C. § 103.

Rejection of Claims 114, 115, 117, 118 and 122-124 Under 35 U.S.C. § 103:

The Examiner has rejected Claims 114, 115, 117, 118 and 122-124 under 35 U.S.C. § 103, contending that these claims are unpatentable over U.S. Patent No. 6,242,570 in view of Mapelli et al., for the reasons of record.

Claims 114, 115, 117, 118 and 122-124 have been cancelled, without prejudice to or disclaimer of the subject matter therein. Accordingly, this rejection is moot, and the Examiner is respectfully requested to withdraw the rejection of Claims 114, 115, 117, 118 and 122-124 under 35 U.S.C. § 103.

Rejection of Claim 105 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claim 105 under 35 U.S.C. § 105 under 35 U.S.C. § 112, second paragraph, contending that this claim lacks proper antecedent basis because Claim 90 does not contain dimeric fusion protein.

Claim 105 has been amended to provide proper antecedent basis and accordingly, the Examiner is respectfully requested to withdraw the rejection of Claim 105 under 35 U.S.C. § 112, second paragraph.

Applicants have attempted to respond to all of the Examiner's concerns as set forth in the June 27 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has any further questions or concerns regarding the claims, please contact the below-named agent at (303) 863-9700 to expedite prosecution.

Respectfully submitted,

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